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## AUTHOR RESPONSE

We appreciated learning that zika-induced microcephaly does not occur in some zika-endemic areas. The history of zika might explain why the prevalence of zika-induced microcephaly incidence is rare in some areas of Asia and Africa. The zika virus was first identified in Africa in 1958.[1] During the 1950s, zika infections in humans were described as mild, self-limited, modestly febrile illnesses with maculopapular cutaneous eruptions.[2] Zika virus infections in Asia were documented during 1966,[3] but the 2007 epidemic in Micronesia also included conjunctivitis, pharyngitis, cephalgia, and arthralgia.[4] The 2013 to 2014 epidemic in French Polynesia revealed a dangerous association between zika infection and Gullian-Barre syndrome and meningoencephalitis.[5] The Brazilian 2015 outbreak evidenced zika as etiology for gestational microcephaly, mental retardation, and neurologic and/or other congenital anomalies.[6]

The zika virus evolved from a mild, localized condition to a serious public health crisis involving huge numbers of people in the world. Alteration in the pattern and effects of this viral infection might be related to replication and transcription changes newly becoming part of its genetic profile.[7] The pre-membrane precursor (prM) protein of the zika virus is documented with greater variability when comparing the virus in Asian humans to those in African mosquitoes. That variability could contribute to structural differences in the virus. Amino acid or nucleotide variations might induce neurotropism, heightened transmissibility, and mosquito vector infectivity to humans.[7] Sequence variations can mediate specific alterations in the prM protein, which affect virulence and might partially explain why it spread to human populations in the Americas.[7]

More rare occurrences of microcephaly could be related to population factors, viral mutations, immunity in the population, herd immunity induced by endemic long-term presence of the virus, and/or low sensitivity of surveillance systems. A zika outbreak causing congenital microcephaly in Brazil was evident.[6] In a retrospective assessment of infected infants, it was documented that despite absence of microcephaly at birth, some infants with laboratory evidence of zika virus infection evidenced brain anomalies associated with a congenital zika syndrome. Neuroimaging revealed ventriculomegaly, decreased brain volumes, cortical malformations, and subcortical calcifications.[8] Time will clarify the future patterns of zika virus existence and its effects on humans.

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